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Introduction: Workshop on the Methodology for Assessing Health Risks from Complex Mixtures in Indoor Air

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There is an increasing awareness and concern that the indoor environment may play a critical role in regard to the scope of exposure of an individual to a broad spectrum of constituents (both chemical and microbial), a number of which may have major toxicological significance. Indoor air may be polluted by a host of toxins produced indoors and depending on particle size and air-exchange rate, by particles infiltrating from outdoors. Additionally, there is increasing evidence that a significant number of cases of poor indoor air quality are the result of energy-saving practices largely implemented since the 1970s, coupled with inadequate design, operation, and maintenance of ventilation and filtration. Significant levels of both chemical and biological contaminants have been frequently associated with the cleanliness of the heating, ventilation, and air conditioning systems.

A number of World Health Organization working groups concerned with the public health impact of indoor air pollutants (*1–3*), and other review bodies such as the National Academy of Science's Committee on Indoor Air Pollutants (*4*), have cited volatile organic compounds (VOCs) as an important category of indoor air pollutants. Title IV of the Superfund Amendments and Reauthorization Act of 1986 (SARA) requires the United States Environmental Protection Agency (EPA) to establish a research program with respect to radon gas and indoor air quality, to disseminate information on indoor air quality, and to disseminate information on indoor air quality problems and solutions (*5*).

Indoor concentrations of total suspended particles and respirable particulates often exceed outdoor concentrations, and agents have been reported to cause both specific illnesses and the broad spectrum of complaints, which constitute the sick-building syndrome. The World Health Organization (*2*) in 1983 defined the sick-building syndrome concept as being characterized by a high frequency of irritative symptoms of the eyes, throat and lower airways, skin reactions, nonspecific hypersensitivity, mental fatigue, headache, nausea, and dizziness among individuals staying in a particular building. The etiology of this syndrome is currently not fully understood. Historically, such environmental hazards have focused on chemical constituents. However, biological contaminants in indoor air are predominantly responsible for known building-related illnesses, which include Legionnaires disease and hypersensitivity pneumonitis (*5*).

Reports concerning discomfort and miscellaneous health effects in relation to nonindustrial workplaces, e.g., office environments, have increased dramatically, especially during the last decade. Indeed, the term "sick-building syndrome" has already become part of the everyday lexicon in many quarters. Additionally, multiple chemical sensitivity (MCS) is also being given wide currency, although clinical manifestations and diagnoses have not been agreed upon. This area is a source of continuing controversy both within the scientific and medical community and the public. At a recent meeting in March 1991, organized by the National Research Council, this controversy over MCS was explored in more detail in an attempt to define criteria for case evaluations, potential for induction of MCS, and to develop epidemiology studies (*6,7*).

A question that is raised is whether it is possible to distinguish between sensitivity resulting from chemicals from indoor air exposures and sensitivity from bacteria, food, or allergens such as dust. The belief is widely held that it is currently difficult to distinguish between these two situations since no "marker" for such sensitivity exists and chemical sensitivity may or may not evoke an immune system response. The nature and extent of chemical sensitivity has been debated by medical experts for years. Additionally, the role of "adaptation" in chemical or bacterial sensitivity is currently not well characterized but may represent developed tolerance under exposure conditions. A number of agents often found in indoor environments are mostly known to be hazardous in high concentrations, but the lower limits of their dose–response relationships are poorly defined. Among the specific problem pollutants are radon, asbestos, environmental tobacco smoke, formaldehyde, chlorinated solvents, and pesticides. Little is known about cancer and noncancer health effects that may be associated with low-level respiratory exposures to these pollutants or to multiple chemical contaminants. While greater efforts are being made to characterize noncancer health effects from various exposure routes, information on exposures in homes and buildings is limited.

Although the magnitude of indoor air health hazards is not now known, mounting evidence suggests that identification of the agents in complex admixtures, a more definitive clinical measure,

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and etiology of their health effects are all critical for a more realistic assessment of the effects of complex mixtures in indoor air for human health. This facet is underscored by studies of human activity-pattern studies, which indicate that individuals spend the majority of their time (e.g., 60–90%) in indoor environments, both at work and at home.

In EPA's Report to Congress on Indoor Air Quality (5), it was noted that indoor air quality research problems and solutions had not been sufficiently characterized to be able to suggest regulatory approaches. However, it was further noted that sufficient evidence exists as described above to conclude that indoor air pollution represents a major portion of the public's exposure to air pollution and may pose serious acute and chronic health risks (5). In recognition of the increasing awareness and concern about the quality of indoor air and its effects on human health, the workshop "Methodology for Assessing Health Risks From Complex Mixtures in Indoor Air" was held in Arlington, Virginia, April 17–19, 1990, and was cosponsored by EPA and ILSI Risk Science Institute. The purpose of the workshop was to provide an overview of the methodology for assessing health risks from complex mixtures in indoor air to a diverse audience including scientists from Federal and State health agencies, the private sector, clinicians, industrial hygienists, and environmental scientists. The members of the Organizing Committee for the workshop were drawn from the scientific, medical, research, and regulatory committee (see Appendix).

The major objectives of the workshop as developed by the Organizing Committee were to be: *a*) define the state-of-the-art in the methodology for assessing health risks from complex mixtures; *b*) describe the varied sources and management of indoor air mixtures; *c*) address the question of whether the problem of complex mixtures in indoor air poses different issues from traditional risk assessment; and *d*) identify future directions and research needs to better assess potential health risks.

The workshop consisted of presentations and panel discussions by researchers from academia, government, and private institutions. Twenty-eight papers were presented in the workshop. Twenty of these papers, as well as the panel discussion, are published in this issue of *Environmental Health Perspectives*.

The workshop consisted of six sessions and a panel discussion. The first session dealt with a broad perspective of the sources and management of indoor air mixtures and featured presentations by L. A. Wallace on a comparison of risks from outdoor and indoor sources and management of indoor air mixtures, followed by a discussion by J. E. Woods on the engineering aspects of indoor air quality control and an elaboration of sources; and exposures to volatile organic compounds in the indoor air environment by P. B. Ryan. P. Koutrakis described indoor air exposures to aerosols and gases; R. Burrell discussed the role of microbiological agents as health risks in indoor air.

The second session was devoted to a description of the adverse health effects encountered in individuals who are sensitive to or susceptible to the effects of air pollutants. Such sensitivity may be to specific pollutants or classes of pollutants, while some individuals may be uniquely sensitive to many irritants. Most will agree that it is usually extremely difficult to unambiguously determine the cause of such sensitivities. Four categories, e.g., hypersensitivity pneumonitis, asthma and allergic rhinitis, infectious syndromes, and dermatitis can account for many cases of reported studies, while a large number of building-related health complaints consist of annoyance or mucous membrane irritation effects, which are often difficult to demonstrate objectively.

M. D. Lebowitz assessed the health effects due to complex mixtures in populations at risk, with a focus on respiratory effects, and R. Bascom highlighted the upper respiratory tract mucosal irritation syndrome. Allergic reactions to indoor air pollutants were described by M. H. Karol; J. E. Cone delineated the health effects of diverse indoor odorants. The sociocultural impacts of toxic contamination, which are increasingly noted in general for environmental contamination, were described by S. Couch. L. S. Welch focused on the overall severity of health effects that can result from poor indoor air quality.

The third session of the workshop dealt with the methodological evaluation of health effects and featured presentations by J. M. Samet on epidemiological approaches for complex mixtures in indoor air and by M. D. Lebowitz on methods to assess respiratory effects of complex mixtures. C. S. Rose discussed a clinical investigation of building-related hypersensitivity pneumonitis. The area of complex mixtures in industrial workplaces was addressed by B. E. Lippy, who focused on lessons that could be drawn from this environment that are relevant for indoor air quality considerations. Applications of short-term bioassays employing hamsters or rats exposed to dusts by either inhalation on intratracheal instillation was addressed by J. D. Brain.

The fourth session focused on biomarkers of health effects, an area that is generally acknowledged to be vital for early recognition of the potentially deleterious effects to individuals exposed to poor-quality indoor environments. R. F. Vogt delineated a variety of tests as biomarkers for human immune status and function. K. I. Bolla stressed the neuropsychological aspects and assessment for the detection of adverse effects on the central nervous system.

Case studies constituted the core of session five. J. A. J. Stolwijk initially presented an overview of the sick-building syndrome. I. Broder discussed formaldehyde exposure and health status in households; R. E. Honicky addressed the respiratory effects of wood heat as delineated by clinical observations and epidemiological assessment.

Four other case reports were presented at the workshop: B. P. Leaderer, assessing exposure to environmental tobacco smoke and pregnancy outcome; B. S. Hulka, markers of exposure and health effects of environmental tobacco smoke; J. L. Davidson, health effects associated with the installation of new carpeting; and D. A. Otto, human reactions to low-level volatile organic compound mixtures found in indoor environments, but are not presented in this issue.

The sixth session dealt with a development of a risk assessment framework. C. R. Shoaf described methodologies for assessing health effects of multiple air pollutants, and a risk characterization framework for noncancer end points was presented by T. K. Pierson.

A panel discussion considering approaches for assessing health risks was chaired by C. J. Henry and energetically carried out by P. A. Schulte, W. J. Meggs, P. J. Lioy, R. O. McClellan, H. Anderson, N. A. Ashford, J. S. Osborne, and D. W. Sepkovic. The objectives of the panel session were to react to the information presented at the workshop; establish priorities for the elements necessary in assessing risks; identify data gaps and research needs; and attempt to address whether complex mixtures found in indoor air exposures lend themselves to "traditional" risk assessment procedures (e.g., employing cancer as an end point or additivity of risk procedures) or whether other approaches need to be explored.

W. H. Farland closed the workshop with a delineation of future directions and research needs addressing EPA's program, as well as providing a synthesis of directions and needs suggested from the presentations and panel discussion. The five major areas that constitute the current EPA indoor air research strategy are: *a*) monitoring/building studies: the development and validation of diagnostic protocols, analytical techniques and comprehensive large building models; *b*) health effects: identify or develop sensitive functional or physiological measures, identify or develop sensitive functional or physiological measures, identify and characterize chemically sensitive individuals and population subgroups, conduct cross-species extrapolation studies, and develop and apply methods for biomonitoring; *c*) source characterization/mitigation: develop methods for measuring pollutant emissions, enlarge EPA's database on sources and emissions, and develop methods for evaluating air cleanness, source control options, and ventilation strategies; *d*) health impact/risk assessment; and *e*) program management/technology transfer. It was considered extremely important to initiate collaboration between the public and private sectors with regard to augmenting this research and data collection.

Appendix

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